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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/030,497   | 06/27/2002  | John C. Reed         | P-LJ 5137           | 2174             |
| 41552  | 7590        | 11/02/2005           | EXAMINER            |                  |
| MCDERMOTT, WILL & EMERY<br>4370 LA JOLLA VILLAGE DRIVE, SUITE 700<br>SAN DIEGO, CA 92122 |             |                      | SANG, HONG          |                  |
|  |             | ART UNIT             |                     | PAPER NUMBER     |
|  |             | 1643                 |                     |                  |
| DATE MAILED: 11/02/2005  |             |                      |                     |                  |

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/030,497             | REED, JOHN C.       |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Hong Sang              | 1643                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 23 September 2005.

2a) This action is FINAL.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 51-88 is/are pending in the application.

4a) Of the above claim(s) 55-57,69-71 and 78-88 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 51-54,58-68 and 72-77 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

|   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>8/5/02</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

**RE: Reed**

1. Applicant's election with traverse of Group I (claims 51-54 and 58-63) and species election of BAG-1 in the reply filed on 9/23/05 is acknowledged. The traversal is on the ground(s) that while the claims of Groups I, III and V are patentably distinct, it is submitted that a thorough search of the claims of any of these groups will likely reveal art relevant to the examination of the claims of the other group. Upon further consideration, Group III is rejoined with Group I. The restriction for Group V is maintained for the reasons below.

Groups I and III are patentable distinct from Group V because they have different steps. Group V encompasses a step of determining a second BAG gene expression level, which is not required for any of the Groups I and III. Different steps require different searches, therefore searching is not coextensive. The requirement is still deemed proper and is therefore made FINAL.

2. The information disclosure statement (IDS) filed on 8/5/2002 has been considered. A signed copy is attached hereto.

3. Claims 51-88 are currently pending. Claims 55-57, 69-71 and 78-88 are withdrawn from further consideration as being drawn to nonelected inventions. Claims 1-50 are cancelled.

4. Claims 51-54, 58-68, and 72-77 are under examination.

5. Due to restriction and species election, for the art rejection claims 51-54, 58-68 and 72-77 are examined to the extent that a BAG gene is BAG-1.

***Specification***

6. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 119(e), 120, 121 and 365(c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application (s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. \_\_\_" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application". Appropriate correction is required.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 51-54, 58-68, and 72-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining

the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate cancer comprising determining a BAG-1 gene expression level in a cancerous prostate tissue and comparing said BAG-1 gene expression level in said patient to a reference BAG-1 gene expression level, does not reasonably provide enablement for a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate cancer comprising determining any and all BAG gene expression level in a cancerous prostate tissue and comparing to any and all BAG gene reference level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

*The nature of the invention*

Claims are drawn to a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a

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prognosis in a patient suffering from prostate comprising determining a BAG gene expression level in a cancerous prostate tissue.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

*The breadth of the claims.*

Claims are drawn to a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate cancer comprising determining a BAG gene expression level in a cancerous prostate tissue. The BAG gene encompasses the art known proteins BAG1, BAG2, BAG3, BAG4, BAG5, BAG7, the isoforms thereof, as well as the BAG genes yet to be discovered.

*Quantity of experimentation*

The quantity of experimentation in this area is extremely large since there is significant variability in the structure and effects of the different BAG genes. Moreover, it would require significant study to determine which of the BAG genes are up regulated or down regulated in prostate cancer and in fact can be used as a prognosis marker for prostate cancer. The identification and characterization of each of these BAG genes would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

*The unpredictability of the art and the state of the prior art*

The art teaches that BAG-1, BAG-3 and BAG-4 of the BAG protein family are overexpressed in certain cancers and the cancer prognosis using BAG gene expression level is not predictable. Liao et al. (FEBS Letters, 2001, 503: 151-157) teach BAG-3 and BAG-4 are over expressed in pancreatic cancer (see abstract and page 152, 2<sup>nd</sup> paragraph). Tang et al. (Journal of Clinical Oncology, 1999, 17(6): 1710-1719, IDS) teach that increased BAG-1 expression was significantly associated with shorter disease free and overall survival in all stages of breast cancer (see table 4, page 1718). Further, Zapata et al. (Breast Cancer Research and Treatment, 1998, 47: 129-140, IDS) teach that BAG-1 levels are higher in invasive breast cancers (page 138, 1<sup>st</sup> column, 3rd paragraph). However, in early-stage breast cancer the increased BAG-1 expression is correlated with good prognosis i.e. overall survival and distant disease free survival (Turner et al. Breast Cancer Research and Treatment, 1997, 46(1): 69). Therefore, the art teaches that increased levels of BAG expression do not always indicate decreased risk of metastasis or recurrence for breast cancer.

*Working examples*

The specification teaches that increased levels of BAG-1 gene expression determined by measuring BAG-1 proteins using an anti-BAG-1 monoclonal antibody provides prognostic information about prostate cancer patients including information about progression to hormone-refractory disease, and the higher intensity of BAG1 immunostaining is associated with a higher incidence of metastatic relapse after therapy (see pages 40-42).

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The specification further teaches that increased levels of BAG-1 gene expression determined by measuring BAG-1 proteins using an anti-BAG-1 monoclonal antibody provides prognostic information about early breast cancer patients (stage I and II), and the higher intensity of BAG1 immunostaining is associated with favorable prognosis (longer survival) (see pages 31-35).

In view of the teaching of the specification, one can draw a conclusion that the cancer prognosis using BAG-1 protein level is not predictable. The higher intensity of BAG1 immunostaining is associated with either unfavorable prognosis (e.g. for prostate cancer) or favorable prognosis (e.g. breast cancer).

*Guidance in the specification*

The specification teaches a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate cancer comprising determining a BAG-1 gene expression level in a cancerous prostate tissue. The specification fails to provide any guidance on a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate cancer comprising determining any other BAG gene expression level in a cancerous prostate tissue. Specification provides no guidance and objective evidence to indicate to one of skill in the art that the any and all BAG genes except BAG-1 gene would be enabling to provide prognosis information of prostate cancer.

*Level of skill in the art*

The level of skill in the art is deemed to be high.

*Conclusion*

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example which teach how to use any and all BAG gene except BAG-1 gene for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 51-54, 58-68, and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Froesch et al. (Proceedings of the American Association for Cancer Research Annual Meeting, March, 1998, 89: 13, print) in view of the teachings of Zapata

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et al (Breast Cancer Research and Treatment, 47: 179-140, IDS), and Sano et al. (US patent NO. 5,665,539, IDS).

Claims are drawn to a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, and a method for determining a prognosis in a patient suffering from prostate, said method comprising: (a) determining a BAG gene expression level in a cancerous prostate tissue sample form said patient, (b) comparing said BAG gene expression level in said patient to a reference BAG gene expression level, wherein said reference BAG gene expression level being a level of BAG gene expression above which correlates with increased risk of tumor recurrence or spread, or decreased survival, below which correlates with a decreased risk of tumor recurrence or spread or increased survival.

Claims are further limited wherein said tumor spread comprises tumor metastasis, said BAG gene expression level is determined by measuring a BAG-1 protein level, said BAG protein level is determined with an antibody specific for BAG protein, said BAG gene encodes a nuclear BAG protein, said BAG gene encodes a cytosolic BAG protein, said BAG gene encodes a protein BAG-1, said BAG gene expression level is determined using an immunoassay, said survival is overall survival, said survival is distant metastasis free survival, said immunoassay is immuno-PCR assay, and said reference BAG gene expression level is a level of BAG gene expression above which correlates with increased risk of tumor recurrence or spread in a first group of patients compared to a second group of patients, said second group of patients having BAG gene expression levels below said reference level.

Froesch et al. teach that BAG-1 protein (cytosolic BAG protein) is expressed in all 9/9 prostate cancer cell lines and 51/51 archival prostate tumor specimens, and BAG-1L protein (nuclear BAG protein) is expressed in prostate cancers and enhances androgen receptor function (see abstract and title). Froesch et al teach detection of BAG-1 and BAG-1L proteins using immunoblotting, immunochemistry and immunoprecipitation.

Froesch et al. do not teach the step of comparing said BAG gene expression level in said patient to a reference gene expression level. Froesch et al do not teach that comparing the BAG gene expression level of two groups of patients to a reference gene expression level, where the BAG gene expression level of the first group is higher than reference BAG gene expression level and that of the second group is lower than the reference BAG gene expression level. Moreover Froesch et al. do not teach an immuno-PCR assay. However these deficiencies are made up for in the teachings of Zapata et al, and Sano et al.

Zapata et al. teach a method of determining overall survival and risk of recurrence of all stages of breast cancer by determining levels of the BAG-1 protein and correlating increased BAG-1 protein expression with decreased overall survival or increased risk of recurrence (see page 138, 3<sup>rd</sup> paragraph). The immunointensity was compared between normal mammary epithelium and adjacent carcinoma in situ or invasive cancer using 20 breast cancer biopsies (see page 134, 135, tables 2-3), where direct side by side comparisons were made between the intensity of the immunostaining

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among the immunopositive cells within normal mammary epithelium, carcinoma in situ and invasive cancers (see page 136, 2<sup>nd</sup> paragraph).

Sano et al. teach detection of a protein using immuno-PCR (see abstract).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Froesch et al., Zapata et al. and the detection techniques of Sano et al. and one would have been motivated to do so because Froesch et al. detected BAG-1 protein in all 9/9 prostate cancer cell lines and all 51/51 prostate tumor specimens and Zapata et al. teaches a method of using a BAG-1 protein as a breast cancer prognosis marker. One would have been motivated to combine the methods of Froesch et al., Zapata et al. and the detection techniques of Sano et al. because Sano et al. teach that immuno-PCR is a useful and efficient method for protein detection. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success of detecting BAG-1 using immuno-PCR and further determining the risk of tumor recurrence, spread or survival in a patient suffering from prostate cancer because Froesch et al already successfully detected BAG-1 protein in all 9/9 prostate cancer cell lines and all 51/51 prostate tumor specimens, Zapata et al. teach a method for prognosis of breast cancer using BAG-1 protein expression level, and the immuno-PCR was already a well-established method for protein detection at the time the invention was made. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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***Conclusion***

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hong Sang  
Art Unit: 1643  
Oct. 25, 2005

  
LARRY R. HELMS, PH.D.  
SUPERVISORY PATENT EXAMINER